

PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: TIEDJE *et al.*

Serial No.: 10/073,464

Group No.: 1634

Filed: 02/11/2002

Examiner: Bausch, Sarae L

Entitled: Microbial identification chip based on DNA-DNA hybridization

APPELLANTS BRIEF
APPEAL NO.:

Mail Stop: Board of Patent Appeals And Interferences
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Dated: August 25, 2006

By:

Traci E. Light

Sir or Madam:

Enclosed please find an Appellants Brief, relating to the above referenced patent application. Also enclosed is a check in the amount of \$250.00 to cover the cost for filing a brief.

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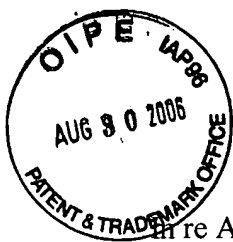
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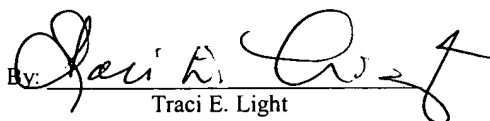
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August 25, 2006

By: 
Traci E. Light

Sir or Madam:

This Brief is in furtherance of the Notice of Appeal mailed on June 27, 2006.

The fees required under § 1.17(c) are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted as a single copy as per the amended rules. [37 CFR § 41.37(a).]

This Brief contains these items under the following headings and in the order set forth below [37 CFR § 1.192(c)].

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I. REAL PARTY IN INTEREST

The real party in interest is Michigan State University, 238 Administration Building East Lansing, Michigan 48824-1046.

II. RELATED APPEALS AND INTERFERENCES

There are no related applications pending appeal.

III. STATUS OF CLAIMS

1. (Appealed) A method of identifying bacteria, comprising:

a) providing:

- i) amplified genomic sequences from a plurality of bacterial species, wherein said amplified genomic sequences are arrayed on a solid support so as to create a plurality of arrayed elements,
- ii) labeled target DNA from a test bacteria of interest, wherein said labeled target DNA is labeled with a fluorescent dye and
- iii) labeled reference DNA from at least four strains of reference bacteria, wherein said reference bacteria are members of the group consisting of said plurality of bacterial species, wherein said labeled reference DNA is labeled with a fluorescent dye;

b) hybridizing said target DNA and said reference DNA to produce a hybridization pattern on said plurality of arrayed elements, wherein each hybridized target DNA in said hybridization pattern has a fluorescent target signal, and each hybridized reference DNA in said hybridization pattern has a fluorescent reference signal; and

c) calculating the hybridized target DNA fluorescent dye signal and reference DNA fluorescent dye signal at each array element to determine the identity of said test bacteria.

2. (Appealed) The method of claim 1, wherein said test bacteria are from a sample obtained from a subject.

3. (Appealed) The method of claim 1, wherein said test bacteria are pathogenic organisms.
4. (Appealed) The method of claim 1, wherein said test bacteria are environmental isolates.
5. (Appealed) The method of claim 1, wherein said solid support is a microchip.
6. (Appealed) The method of claim 1, wherein said calculating comprises statistical analysis.
7. (Cancelled)
8. (Appealed) The method of claim 1, further comprising the step of producing hybridization profiles of said test and reference bacteria.
9. (Appealed) A method of identifying bacteria, comprising:
 - a) providing:
 - i) amplified genomic sequences from a plurality of bacterial species, wherein said amplified genomic sequences are arrayed on at least one microchip, so as to create a plurality of arrayed elements,
 - ii) labeled target DNA from a test bacteria of interest, wherein said labeled target DNA is labeled with a fluorescent dye and
 - iii) labeled reference DNA from at least four strains of reference bacteria, wherein said reference bacteria are members of the group consisting of said plurality of bacterial species; wherein said labeled target DNA is labeled with a fluorescent dye;
 - b) hybridizing said target DNA and said reference DNA to produce a hybridization pattern on said plurality of arrayed elements, wherein each hybridized target DNA in said hybridization pattern has a fluorescent

target signal, and each hybridized reference DNA in said hybridization pattern has a fluorescent reference signal;

- c) calculating the hybridized target DNA fluorescent dye signal and reference DNA fluorescent dye signal at each array element to determine the identity of said test bacteria.

10. (Appealed) The method of claim 9, wherein said test bacteria are from a sample obtained from a subject.

11. (Appealed) The method of claim 10, wherein said test bacteria are pathogenic organisms.

12. (Appealed) The method of claim 9, wherein said test bacteria are environmental isolates.

13. (Appealed) The method of claim 9, further comprising the step of producing hybridization profiles of said test and reference bacteria.

14. (Appealed) The method of claim 9, wherein said calculating comprises statistical analysis.

15-21. (Cancelled)

IV. STATUS OF AMENDMENTS

All amendments in the case have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention relates to methods for identifying bacteria. Further, bacteria may be identified by using amplified genomic sequences on a solid support (i.e., for example, an array).

In independent Claim 1, amplified genomic sequences from a plurality of bacterial species (pg 7 ln 3-26) are arrayed on a solid support (pg 3 ln 5) and hybridized to a fluorescently labeled target DNA (pg 33 ln 8-22) from a test bacteria (pg 6 ln 23-24; and pg 12 ln 9-12) and a fluorescently labeled reference DNA (pg 33 ln 8-22) from at least four different bacterial strains (pg 11 ln 25 – pg 12 ln 2). In a second step, a calculation compares the target DNA fluorescent signal with the reference DNA fluorescent signal (pg 6 ln 25 – pg 7 ln 22; and pg 8 ln 11 – pg 10 ln 11). This embodiment is further defined wherein; i) the test bacteria is obtained from a subject (see Claim 2; pg 13 ln 11-12); ii) the test bacteria is pathogenic (see Claim 3, pg 3 ln 12); iii) the test bacteria is isolated from the environment (see Claim 4, pg 14 ln 3-6); iv) the solid support is a microchip (see Claim 5, pg 3 ln 18); v) the calculation is performed using statistical analysis (see Claim 6, pg 6 ln 16-17; and pg 33 ln 25 – pg 37 ln 18); and vi) the method further comprises producing test/reference bacteria hybridization profiles (see Claim 8, pg 6 ln 27-29).

In independent Claim 9, amplified genomic sequences from a plurality of bacterial species (pg 7 ln 3-26) are arrayed on at least one microchip (pg 3 ln 18) and hybridized to a fluorescently labeled target DNA (pg 33 ln 8-22) from a test bacteria (pg 6 ln 23-24; and pg 12 ln 9-12) and a fluorescently labeled reference DNA (pg 6 ln 25 – pg 7 ln 22; and pg 8 ln 11 – pg 9 ln 11) from at least four different bacterial strains (pg 11 ln 25 – pg 12 ln 2). In a second step, a calculation compares the target DNA fluorescent signal with the reference DNA fluorescent signal (pg 6 ln 25 – pg 7 ln 22; and pg 8 ln 11 – pg 10 ln 11). This embodiment is further defined wherein; i) the test bacterial is obtained from a subject (see Claim 10; pg 13 ln 11-12); ii) the test bacteria is pathogenic (see Claim 11, pg 3 ln 12); iii) the test bacteria is isolated from the environment (see Claim 12, pg 14 ln 3-6); and vi) the method further comprises producing test/reference bacteria hybridization profiles (see Claim 13, pg 6 ln 27-29); and v) the calculation is

performed using statistical analysis (see Claim 14, pg 6 ln 16-17; and pg 33 ln 25 – pg 37 ln 15).

VI. GROUNDS OF REJECTION TO BE REVIEWED UPON APPEAL

- .A. Whether Claims 1-5 and 8-13 are properly rejected under 35 USC § 103(a) over *Kuipers O.P.*, *Current Opinion In Biotechnology*, 10:511-516 (1999) and *Greisen et al.*, *J. Clinical Microbiology*, 32:335-351 (1994).
- B. Whether Claims 6 and 14 are properly rejected under 35 USC § 103(a) over *Kuipers O.P.*, *Current Opinion In Biotechnology*, 10:511-516 (1999) and *Greisen et al.*, *J. Clinical Microbiology*, 32:335-351 (1994) as applied to Claims 1-5 and 8-13 above, and further in view of *Arfin et al.*, *Journal Of Biological Chemistry*, 275:29672-29684 (2000).

VII. ARGUMENT

In summary, the Applicants rebut the Examiner's assertion of obviousness to the presently claimed embodiments. The Applicants argue that the Examiner has not shown that the cited references contain any suggestion that the teachings within the cited references should be combined. Moreover, even when taken in combination the combined references fail to teach all the claimed elements. Further, none of the cited references provide any expectation of success that the Applicants' claimed embodiments would work. Indeed, the Applicants submit that the Examiner's rejections appear arbitrary and are not based upon teachings provided by one having ordinary skill in the art or other evidence.

The Applicants note that the Examiner has misapplied *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); and *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) by stating that:

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

Office Action Mailed March 27, 2006, pg. 3. The Examiner has grossly mischaracterized the court's meaning regarding *In re Keller* and *In re Merck & Co.* by not properly placing the above conclusion in its intended legal context.¹

Specifically, the Examiner fails to realize that *In re Keller* was decided upon an affidavit that discussed only one of three cited references:

As characterized by appellant, the Cywinski affidavit offered as objective evidence of non-obviousness "concerns itself mainly with the question of whether the Walsh et al. article suggest[sic] the use of ..." ... In the present case, we are not presented with a single prior art reference, but rather two combinations of three references. ... The affidavit does not indicate that Dr. Cywinski ... critically reviewed ... the two combinations of references.

In re Keller, 642 F.2d 413, 425-426, 208 USPQ 871 (CCPA 1981). Similarly, the citation relied upon by the Examiner within *In re Merck & Co.* supports a finding by the Federal Circuit that the presentation of a non-obviousness argument to only one cited reference (out a total of nine) is insufficient to overcome an obviousness rejection:

We also find untenable appellant's arguments that Petersen teaches away from appellants' invention. ... Thus, Petersen must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole.

In re Merck & Co., 800 F.2d 1091 1097, 231 USPQ 375 (Fed. Cir. 1986). This is not the case here. The Applicants' previous response provided an organized argument regarding each of the three references AND an integrated conclusion. Clearly, the Applicants' response to the Examiner's obviousness rejection does not fall within the scope of *In re Keller* or *In re Merck & Co.*²

¹ The Applicants respectfully submit that this appeal offers the chance for the Board to educate all Examiner's on the holdings of this particular case, as it is routinely misused.

² If *Keller* or *Merck* are interpreted in the manner of the Examiner, they conflict with more modern cases, including Federal Circuit precedent stating that references must be evaluated individually for their specific motivation to one skilled in the art, without hindsight, before the combination can be made. *In re Rouffet*, 149 F.3d 1350, 476 USPQ2d 1453, 1458 (Fed. Cir. 1998).

A. There Is No *Prima Facie* Case Of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness. The Board is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejections do not meet these criteria. The Applicants rebut the establishment of a *prima facie* case of obviousness by the arguments below.

As a preliminary matter, when dealing with a rejection based upon obviousness it is essential for the PTO to view the claimed embodiment as a whole:

[T]he question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious. Consideration of differences, like each of the findings set forth in *Graham*, is but an aid in reaching the ultimate determination of whether the claimed invention as a whole would have been obvious.

Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1537, 218 USPQ 871 (Fed. Cir. 1983) (emphasis in the original). It is clear to the Applicants that the Examiner has not "stepped back" from the elements to actually "see" the claimed embodiment.

Further, the Examiner uses the Applicants' specification in hindsight. The Federal Circuit has noted that:

The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification.

In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992). The Applicants note that the Examiner's conclusions allegedly establishing a *prima facie* case of obviousness are not supported by cited references. The Applicants show below that *Kuipers* and *Greisen et*

al. represent an improper 35 USC 103(a) reference combination, thereby traversing both Examiner's rejections.

B. Rejection Under 35 USC § 103(a) Over Kuipers and Greisen et al.

The Examiner has rejected Claims 1-5 and 8-13 under 35 U.S.C 103(a) as allegedly being unpatentable over *Kuipers O.P., Current Opinion in Biotechnology*, 10:511-516 (1990) and *Greisen et al., J. Clin. Microbiol.* 32:335-351 (1994). We disagree for all the reasons stated below.

1. There Is No Motivation To Combine The Art

The Examiner fails to show any motivation for one having ordinary skill in the art to modify the teachings of *Kuipers* with the teachings of *Greisen et al.* The Examiner is reminded of the above argument showing that *Kuipers* does not disclose a method to identify bacteria comprising differentially fluorescent labeled reference and target DNAs that hybridize to bacterial genomic DNA.

The Applicants argue that *Greisen et al.* teaches the development and use of methods comprising universal primers based upon the well known 16S rRNA gene. The Applicants have pointed out the many art-recognized disadvantages to the 16S rRNA gene detection methods:

Although the 16S rRNA method has served as a powerful tool for finding phylogenetic relationship between bacteria because of its molecular clock properties and the large database for sequence comparison, the molecule is too conserved to provide good resolution at the species and subspecies levels (*See e.g., Woese, Microbiol. Rev.* 51:221-271 [1987]; DeParasis and Roth, *Phytopathol.*, 80:618-621 [1990]; Fox *et al.*, *Int. J. Syst. Bacteriol.*, 42:166-170; Martinez-Murcia *et al.*, *Int J Syst. Bacteriol.*, 42:412-421 [1992]; Stackebrandt and Goebble, *Int. J. Syst. Bacteriol.* 44:846-849 [1994] and Weisburg *et al.*, *J. Bacteriol.* 173:697-703 [1991]).

Applicants' Specification, pg 1 ln 19-27. Because of the general consensus in the art regarding the above enumerated 16S rRNA disadvantages, one having ordinary skill in the art would not use a reference based upon 16S rRNA universal primers (i.e., for example, *Greisen et al.*) to create the Applicants' hybridization method to identify bacteria. Second, *Kuipers* teaches using a single bacterial species (when suggesting that arrays might be useful to compare relative gene transcription rates) and does not suggest

that using a plurality of bacterial species would be advantageous³. Consequently, even if one having ordinary skill in the art were to find *Greisen et al.* and *Kuipers* their respective teachings do not suggest combining one with the other.

2. Not All The Claim Elements Are Taught

Even if the references were properly combined (even though they are not), the reference combination does not teach all the claimed elements.

a. Claim 1

The Examiner has not taught every element of the claimed invention because neither *Kuipers* nor *Greisen et al.* show: i) the hybridization of a fluorescently labeled reference DNA from at least four strains of reference bacteria to a solid support comprising an array of DNA from a plurality of bacterial species; ii) the hybridization of a fluorescently labeled target DNA to a solid support comprising an array of DNA from a plurality of bacterial species; and iii) identifying a bacterial species by calculating data collected from the reference fluorescent label and the test fluorescent label.

The Examiner states that:

Kuipers teaches producing a specific DNA array for the rapid identification of pathogens and spoilage bacteria ... (see page 512, 2nd column, 2nd paragraph).

Office Action Mailed July 1, 2005 pg 7. The Examiner's conclusion is arbitrary because this passage within *Kuipers* is taken out of context. As the Applicants explain below, *Kuipers* does not teach any specific DNA array for the rapid identification of bacteria.

When *Kuipers* is read in its entirety (as it properly should), *Kuipers* clearly states that such DNA bacterial identification arrays are unavailable in the art. Specifically, the Examiner refers to the following sentence:

Of course, specific DNA arrays can be developed for ... rapid identification of pathogens and spoilage bacteria ...

Kuipers, pg 512, 2nd column, 2nd paragraph [emphasis added]. The Examiner is requested to note that *Kuipers* is only inviting one to try to develop a DNA array for this purpose.

³ In a method to compare wild-type and mutant transcription rates, a multi-species array would be deleterious.

Kuipers presents no teachings that demonstrates that it has actually been done, or exactly how it could be done, by anyone. The Examiner is reminded that ‘obvious to try’ and ‘obviousness’ are not equivalent and is well settled patent law:

An invention is not obvious where the prior art gives ‘no direction as to which of many possible choices is likely to be successful.

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 166 F. Supp.2d 19, 36 (D. N.J. 2001), *aff’d*, 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003); and

A finding ... that the patented invention may have been ‘obvious to try’ from the prior art will not invalidate it. Prior art that makes the invention only ‘obvious to try’ rather than ‘obvious’ ‘gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful’.

Bristol-Meyers Squibb Co. v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir. 2001). The Examiner has not pointed to any teachings within *Kuipers* that provides any teachings regarding which bacterial genomes should be utilized, what kind of fluorescent DNA labels are optimum, or how to calculate the data once the fluorescent signals are detected in order to identify any bacterial species. Simply mentioning that such a method “might be possible” sometime in the future is insufficient.

This futuristic tone set by the above *Kuipers* passage is repeated:

With the ever-increasing availability of genome sequences ... genotypic methods that are amenable to automation will be developed. It can be foreseen that DNA microarrays with specific probes for thousands of different species or strains will be developed, enabling fast and reliable identification of microorganisms.

Kuipers, pg 514, 2nd column, 2nd paragraph. Clearly, *Kuipers* is not concluding that these types of microorganism identification methods are already present in the art. As such, the Examiner is not permitted to conclude otherwise.

Further, the Examiner improperly asserts that the *Kuipers* page 512, 2nd column, 1st paragraph teaches the Applicant’s claimed embodiment. *Office Action Mailed July 1, 2005*, pg. 7. The Examiner has improperly argued that the above speculation by *Kuipers*

(page 512, 2nd column, 2nd paragraph) regarding DNA array identification of bacteria is supported by other teachings within *Kuipers* (page 512, 2nd column, 1st paragraph). This is not the case. The Examiner is requested to read the entire 1st paragraph, in context, especially the following sentences:

The data obtained provide information on differential gene expression. In essence, levels of all genes (mRNA converted into labeled cDNA) of the relevant microorganism are measured relative to a standard (e.g., a wild-type strain's expressed genes) by hybridizing the labeled cDNA to the whole cell genome displayed on the DNA microarray.

Kuipers pg 512 2nd column, 1st paragraph [emphasis added]. Clearly, *Kuipers* was not discussing the possibility of identifying bacterial species, but detecting gene transcription levels from a single bacterial species by comparing “wild-type and mutant-strain cDNA”⁴. When a reference clearly discloses a conclusion of one skilled in the art, such as this, the Examiner is not permitted to conclude otherwise.

The above argument shows that *Kuipers* does not teach any methods for identifying bacterial strains based upon hybridizing labeled fluorescent reference DNA from at least four strains of reference bacteria and fluorescently labeled target DNA to DNA from a plurality of bacterial species arrayed on a solid support (i.e., for example, a microarray).

The Examiner also asserts *Greisen et al.* by stating that:

Greisen et al. teaches a method of detecting DNA for the identification of over 60 different strains representing 18 different bacterial species ...

Office Action Mailed July 1, 2005, pg 7. *Greisen et al.* discloses a method that is dependent upon obtaining universal primers from the conserved 16S rRNA gene and is limited to teaching radioactive phosphorous labels (i.e., ³²P). Consequently, as the Examiner admits, *Greisen et al.* does not teach co-hybridizing differential fluorescently labeled target and reference DNAs. *Office Action Mailed July 1, 2005, pg 8.* The Examiner has not pointed to *Greisen et al.* for any teaching except “... 12 different

⁴ The Examiner is reminded that “a strain” is not “a species”.

probes of seven reference bacterial species...”. *Office Action Mailed March 27, 2006, pg. 4.* Consequently, *Greisen et al.* does not teach any methods for identifying bacterial strains based upon hybridizing labeled fluorescent reference DNA from at least four strains of reference bacteria and fluorescently labeled target DNA to DNA from a plurality of bacterial species arrayed on a solid support (i.e., for example, a microarray).

b. Claim 9

The Applicants believe the arguments presented above regarding Claim 1 are sufficient to rebut the Examiner’s rejection of Claim 9. Consequently, in the interest of brevity, the Applicants incorporate by reference the argument presented (above) in Section VII(B)(1)(a). Claim 9 specifies the array is on a microchip. The cited prior art does not contemplate any methods for identifying bacterial strains based upon hybridizing labeled fluorescent reference DNA from at least four strains of reference bacteria and fluorescently labeled target DNA to DNA from a plurality of bacterial species arrayed on a microchip.

c. Claims 2 and 10

The Examiner has not pointed to where either *Kuipers* or *Greisen et al.* teaches that a DNA sample should, or could, be obtained from a subject, fluorescently labeled, and hybridized to a genomic bacterial array comprising a plurality of bacterial species.

d. Claims 3 and 11

The Examiner has not pointed to where either *Kuipers* or *Greisen et al.* teaches that a pathogenic test bacteria should, or could, be fluorescently labeled and hybridized to a genomic bacterial array comprising a plurality of bacterial species.

e. Claims 4 and 12

The Examiner has not pointed to where either *Kuipers* or *Greisen et al.* teaches that test bacteria should, or could, be from an environmental isolate.

f. Claim 5

The Examiner has not pointed to where either *Kuipers* or *Greisen et al.* teaches that a solid support is a microchip for the performance of Claim 1.

g. Claims 8 and 13

The Examiner has not pointed to where either *Kuipers* or *Greisen et al.* teaches a hybridization profile generated from data using a reference fluorescent signal and a target fluorescent signal.

3. There Is No Expectation Of Success

A proper analysis under 35 U.S.C. § 103(a) requires that a combination of references must provide a reasonable expectation of success should the claimed combination be carried out. *MPEP* § 2143.02. Moreover, “both the suggestion and reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Vaeck*, 20 USPQ2d 1438, 1442, 947 F.2d 488 (Fed. Cir. 1991). Neither *Kuipers* nor *Greisen et al.* provide any explicit suggestions that the Applicants’ claimed embodiment would, in fact, work⁵.

The Examiner, instead, simply offers personal interpretations of passages within the cited art, for example:

Furthermore, the ordinary artisan would have had a reasonable expectation of success that using up to 12 different probes to test against seven major bacterial species that cause meningitis could be used in the method of Kuiper et al. [sic] because Kuiper et al. [sic] suggests using different cDNA strains in one sample for multiplexing and allowing for analysis of several different cDNA samples at one time.

Office Action Mailed July 1, 2005, pg 8. As explained above, *Kuipers* does not teach using different cDNA strains in one sample in order to identify a bacteria. The Examiner has merely made a personal opinion that is unsupported by any explicit statements within the cited art. The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (“[T]he examiner’s assumptions do not constitute the disclosure of the prior art.”).

⁵ The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work. *In re O’Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

**C. Rejection Under 35 USC § 103(a) Over Kuipers, Greisen et al.,
in view of Arfin et al.**

The Examiner has rejected Claims 6 and 14 under 35 U.S.C 103(a) as allegedly being unpatentable over *Kuipers O.P., Current Opinion in Biotechnology*, 10:511-516 (1999) and *Greisen et al., J. Clin. Microbiol.* 32:335-351 (1994) in further view of *Arfin et al., J. Biol. Chem.* 275:29672-29684 (2000). We disagree for the reasons previously provided and for all the reasons stated above in regards to the primary combination of *Kuipers* and *Greisen et al.* In the interest of brevity, the arguments presented (above) in Section B are incorporated herein by reference.

1. There Is No Motivation To Combine The Art

The Applicants incorporate by reference the arguments above showing that *Kuipers* and *Greisen et al.* fail to provide any motivation to combine their teachings. The Examiner makes a failed attempt to show a motivation to modify the teachings within either *Kuipers* and/or *Greisen et al.* with *Arfin et al.*

For instance, the Examiner believes that:

Arfin teaches replication and appropriate statistical analysis for determining accuracy of DNA microarray measurements and one of ordinary skill in the art would have modified the teachings of Kuiper and Greisen et al to improve the analysis of identification of bacteria by including statistical analysis of the data to determine the accuracy of the DNA microarray measurements.

Office Action Mailed March 27, 2006, pg. 5 [emphasis added]. Again, the Examiner has usurped the role of “one having ordinary skill in the art” in making this conclusion. More importantly, however, the Examiner has mischaracterized the *Arfin et al.* reference. *Arfin et al.* uses statistical analysis to identify experimental factors that require modification that will result in an improved accuracy of a microarray technique. For example,

These statistical methods allowed us to identify and minimize experimental variables that affect the reproducibility and accuracy of DNA microarray measurements and to determine the statistical significance of observed differences between expression levels of each ORF in these two genotypes.

Arfin et al., pg 29673 2nd column, 1st paragraph [emphasis added]. Clearly, *Arfin et al.* is using a standard ANOVA analysis as a tool to identify ways to optimize a method that only measures gene transcription levels. *Arfin et al.* does not suggest that this statistical analysis could, or should, be used to calculate an expression profile using data from a fluorescently labeled reference DNA and a fluorescently labeled target DNA.

2. Not All The Claim Limitations Are Taught

Even if the references were properly combined (even though they are not), the reference combination does not teach all the claimed elements.

In order to fulfill the deficiencies described above in regards to the deficient teachings of *Kuipers* and *Greisen et al.*, *Arfin et al.* must disclose: i) the hybridization of a fluorescently labeled reference DNA from at least four strains of reference bacteria to a solid support comprising an array of DNA from a plurality of bacterial species; ii) the hybridization of a fluorescently labeled target DNA to a solid support comprising an array of DNA from a plurality of bacterial species; and iii) identifying a bacterial species by calculating data collected from the reference fluorescent label and the test fluorescent label.

The Examiner fails to point out where *Arfin et al.* provides these missing teachings⁶. In particular, *Arfin et al.* does not teach the use of differentially labeled fluorescent reference and target DNAs. In fact, *Arfin et al.* teaches the use of a single type of label (i.e., radioactive phosphorous, ³²P). Further, the statistical analysis taught by *Arfin et al.* cannot be used to calculate data generated from more than one label signal:

To evaluate the data generated by these gene expression profiling experiments we used a linear analysis of variance model appropriate for the experimental design employed in this study.

Arfin et al., pg 29673 2nd column, 1st paragraph. *Arfin's* experimental design did not use more than a single label, therefore, *Arfin et al.* admits that the analysis of variance (ANOVA) model was not constructed with factors to evaluate the variance contribution of more than one label.

⁶ The Examiner is reminded that the Applicants' previously rebutted this rejection by pointing out that *Arfin et al.* is irrelevant to the Applicants' claimed embodiment.

Secondly, *Arfin et al.* does not suggest that more than one bacterial species could, or should, be arrayed. In fact, *Arfin et al.* teaches arrays limited to *E. coli*:

In this report, we describe the use of nylon membranes spotted in duplicate with full-length polymerase chain reaction-generated products of each of the 4,290 predicted *E. coli* K12 ORFs to measure the gene expression profiles ...

Arfin et al., pg. 29673 2nd column, 1st paragraph [emphasis added]. The Examiner should note, that as with *Kuipers*, *Arfin et al.* teaches methods for gene transcription expression, not bacterial species identification.

In conclusion, *Arfin et al.* does not provide any missing elements identified above in regards to the *Kuipers – Greisen et al.* mis-combination.

3. **There Is No Expectation Of Success**

A proper analysis under 35 U.S.C. § 103(a) requires that a combination of references must provide a reasonable expectation of success should the claimed combination be carried out. *MPEP* § 2143.02. Moreover, “both the suggestion and reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *In re Vaeck*, 20 USPQ2d 1438, 1442, 947 F.2d 488 (Fed. Cir. 1991). *Kuipers*, *Greisen et al.*, or *Arfin et al.* do not provide any explicit suggestions that the Applicants’ claimed embodiment would, in fact, work⁷.

The Examiner, instead, simply offers personal interpretations of passages, for example:

Furthermore, *Arfin et al.* teach that thousands of measurements are obtained from a single experiment using DNA microarrays experiments and in order to interpret data from experiments it is necessary to employ statistical methods capable of distinguishing chance occurrences from biologically meaningful data, therefore, the ordinary artisan would have had a reasonable expectation of success of using statistical data analysis in the method of *Kuiper et al.* [sic] and *Greisen et al.*

Office Action Mailed July 1, 2005, pg. 10 – 11. The above paragraph contains no reference to any explicit teachings within *Arfin et al.* that the ANOVA analysis could, or

⁷ The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work. *In re O’Farrell*, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988).

should, be used to calculate data from a fluorescently labeled reference DNA and a fluorescently labeled target DNA. Interestingly, the Examiner's conclusion states that *Arfin et al.* "... would have had a reasonable expectation of success of using statistical data analysis in the method of Kuiper et al. and Greisen et al.". The Applicants have no comment on this conclusion, as the methods described in *Kuipers* and *Greisen et al.* are not those of the presently claimed embodiments.

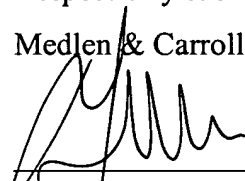
D. Conclusion

Appellants submit that, with due consideration to all these factors discussed above, the patentability of Claims 1-6 and 8-14 is evident. None of the cited references (either alone or in combination) teach any methods to identify bacteria using calculations from a fluorescently labeled reference DNA and a fluorescently labeled target DNA that hybridize to an array of genomic bacterial DNA.

For these reasons, the Applicants now appeal because it appears the Examiner has taken an arbitrary position. It is submitted that the Examiner's rejections of Claims 1-6 and 8-14 were erroneous, and reversal of these rejections is respectfully requested.

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Respectfully submitted,
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VIII. CLAIMS APPENDIX

1. A method of identifying bacteria, comprising:
 - a) providing:
 - i) amplified genomic sequences from a plurality of bacterial species, wherein said amplified genomic sequences are arrayed on a solid support so as to create a plurality of arrayed elements,
 - ii) labeled target DNA from a test bacteria of interest, wherein said labeled target DNA is labeled with a fluorescent dye and
 - iii) labeled reference DNA from at least four strains of reference bacteria, wherein said reference bacteria are members of the group consisting of said plurality of bacterial species, wherein said labeled reference DNA is labeled with a fluorescent dye;
 - b) hybridizing said target DNA and said reference DNA to produce a hybridization pattern on said plurality of arrayed elements, wherein each hybridized target DNA in said hybridization pattern has a fluorescent target signal, and each hybridized reference DNA in said hybridization pattern has a fluorescent reference signal; and
 - c) calculating the hybridized target DNA fluorescent dye signal and reference DNA fluorescent dye signal at each array element to determine the identity of said test bacteria.
2. The method of claim 1, wherein said test bacteria are from a sample obtained from a subject.
3. The method of claim 1, wherein said test bacteria are pathogenic organisms.
4. The method of claim 1, wherein said test bacteria are environmental isolates.
5. The method of claim 1, wherein said solid support is a microchip.

6. The method of claim 1, wherein said calculating comprises statistical analysis.
8. The method of claim 1, further comprising the step of producing hybridization profiles of said test and reference bacteria.
9. A method of identifying bacteria, comprising:
 - a) providing:
 - i) amplified genomic sequences from a plurality of bacterial species, wherein said amplified genomic sequences are arrayed on at least one microchip, so as to create a plurality of arrayed elements,
 - ii) labeled target DNA from a test bacteria of interest, wherein said labeled target DNA is labeled with a fluorescent dye and
 - iii) labeled reference DNA from at least four strains of reference bacteria, wherein said reference bacteria are members of the group consisting of said plurality of bacterial species; wherein said labeled target DNA is labeled with a fluorescent dye;
 - b) hybridizing said target DNA and said reference DNA to produce a hybridization pattern on said plurality of arrayed elements, wherein each hybridized target DNA in said hybridization pattern has a fluorescent target signal, and each hybridized reference DNA in said hybridization pattern has a fluorescent reference signal;
 - c) calculating the hybridized target DNA fluorescent dye signal and reference DNA fluorescent dye signal at each array element to determine the identity of said test bacteria.
10. The method of claim 9, wherein said test bacteria are from a sample obtained from a subject.
11. The method of claim 10, wherein said test bacteria are pathogenic organisms.

12. The method of claim 9, wherein said test bacteria are environmental isolates.
13. The method of claim 9, further comprising the step of producing hybridization profiles of said test and reference bacteria.
14. The method of claim 9, wherein said calculating comprises statistical analysis.

IX. EVIDENCE APPENDIX

(No attachments are required for this Brief)

X. RELATED PROCEEDINGS APPENDIX

(No attachments are required for this Brief)